REMARKS

Claims 7, 15, 16, 18, 20, and 47-82 (including previously withdrawn claims) are canceled without prejudice or disclaimer. Applicants reserve the right to pursue any of the canceled subject matter in one or more continuing applications.

Claims 1-6, 8-14, 17, 19, 21-46 and 83-93 are pending and under examination.

Formal matters

Sequence Compliance

Applicants submit herewith a replacement Sequence Listing in computer readable form as required by 37 CFR §1.824. In addition, applicants submit a replacement paper copy Sequence Listing as required under 37 CFR §1.823(a) and a statement under 37 CFR §1.821(f). The enclosures fulfill the requirements of 37 C.F.R. §§1.821-1.825.

The amendments in the specification merely insert the paper copy of the Sequence Listing and sequence identifiers in the specification. No new matter has been added.

Title

The tile has again been amended to be made more descriptive, as requested by the Examiner.

Claims Objections

Claims 32 and 36 have been amended to depend from a pending claim. No new matter is added.

Rejections Under 35 U.S.C. §112, para. 2

Claims 1-6, 8-15, 17, 19, 21-46, 83 and 90-93 are rejected as indefinite.

Claims 1, and 14 are said to be indefinite in the recitation of "variant thereof". This rejection has been addressed by amending the claims as suggested by the Examiner.

Claims 1, 14 and 83 are said to be indefinite in the recitation of "a functional fragment". This rejection has been addressed by amending the claims to specify that the functional fragment has the specific function of promoting secretion from a cell.

Claim 36 is said to lack proper antecedent basis. Claim 36 has been amended to depend from claim 17, which contains the term "cleavage site".

Claims 19 and 39 are said to be indefinite in the recitation of "mature form". Applicants maintain that the term "mature form" is a term of art that would be clear to a skilled artisan. However, in the interest of expediting prosecution, the claims have been amended to recite that the mature form of the small peptide lacks the signal peptide and pro-region of somatostatin.

Claim 27 is said to be indefinite in the recitation of "the cell...further comprising at least one regulatory sequence". Claim 27 has been amended to recite that the nucleic acid sequence that encodes the fusion protein is operably linked to the "at least one regulatory sequence...", making more clear the relationship between the encoding sequence and the regulatory sequence.

Rejections Under 35 U.S.C. §112, para. 1

Claim 83 is rejected for lack of written description for the term "analog thereof." Claim 83 has been amended to replace the term "analog" with "variant", which is explicitly limited in structure (differs from the wild-type amino acid sequence by at least 1 but not more than 15 amino acid residues) and function (promotes secretion from a cell). Given the specific structural and functional parameters of the recited variant, it would be clear to a skilled person that Applicants were in possession of the claimed subject matter.

Claims 15 and 47-52 are rejected for alleged lack of written description and claim 15 is further rejected for alleged lack of enablement. Applicants disagree with the Examiner's grounds for the rejection. However, in the interest of expediting prosecution, claims 15 and 47-52 are canceled without prejudice.

Rejections Under 35 U.S.C. §103

I. Construct claims

Claims 1-6 and 8-13 are rejected as unpatentable over Sevarino in further view of Stoller, Habener, Susuki and Patel, all of which were cited and discussed in the previous Office Action mailed December 18, 2002 (hereinafter "the first Office Action"). The substance of the rejection is identical to a previous rejection made in the first Office Action, which rejection was already addressed on the merits by amendments and arguments made in the Reply filed June 18, 2003

(hereinafter "the first Reply"), at least with regard to claims 5, 9, 11 and 13. Indeed, it is unclear why the present rejection is again being applied to claims 5, 9, 11 and 13, since the Office Action itself states that the rejection of these particular claims over these cited references was withdrawn. I.e., the present Office Action provides as follows.

> The prior art rejection of claim 5, 9, 11, 13, 31, 35, 37, 46, 52 and 83 under 35 U.S.C. 103(a) as being unpatentable over Severino et al. (Cell, 1989, 57(1): 11-19), and further in view of Stoller et al. (J. Cell Biol., 1989, 108: 1647-55, provided by applicants), Habener et al. (US 5,118,666), Suzuki et al. (US 5,891,671), and Patel et a. (CIBA Foundation Symposium, 1995, 190:26-50), is withdrawn in view of applicant's amendment, however, the amendment necessitated new art rejections set forth below. (Office Action, page 2, emphasis added.)

Therefore, Applicants respectfully request clarification of this rejection.

With regard to claims 1-4, 6, 8, 10 and 12, the Examiner has repeated the substance of the previous obviousness rejection to the newly rejected claims. Although Applicants' arguments rebutting the substance of this rejection are already of record, having been presented in the first Reply with regard to claims 5, 9, 11 and 13, they are repeated below for completeness, as they apply to all of claims 1-6 and 8-13.

The rejection of claims 1-6 and 8-13 is respectfully traversed. As discussed in the first Reply, the claimed constructs include a nucleic acid sequence encoding a small peptide other than somatostatin (e.g., GLP-1). The cited references lack the requisite specific motivation and reasonable expectation of success to combine the references to arrive at the specific claimed constructs. The mere fact that references (in this case, five references) can be combined does not render the resultant combination obvious unless the prior art also evidences the desirability and reasonable expectation of success for the specific combination as claimed. See MPEP § 2143.01. In this case, the Examiner appears to have merely plucked limitations from numerous prior art references and pieced them together using the claims as a template. The Federal Circuit has made it clear that this is impermissible.

The Examiner cites Severino and Stoller to support the proposition that one "reasonably would have expected success because Severino and Stoller have demonstrated successful expression of two different heterologous peptides by using fusing (*sic*) pro-region of

prosomatostatin with the target peptide." However, neither Sevarino's nor Stoller's results are predictive of whether one could successfully express any heterologous (non-somatostatin) small peptide, as claimed. Sevarino expressed a somatostatin from a different source than the pro-region, but a somatostatin nonetheless. Stoller demonstrated expression of a large polypeptide (globin). Neither of these references provides a reasonable expectation that a construct for expression of a heterologous small peptide would be successful. A skilled artisan would be aware, for example, that expression of small peptides involves different technical challenges (such as increased degradation) than expression of larger polypeptides such as globin and would not see Sevarino and Stoller as providing a motivation or reasonable expectation of success to make the claimed constructs.

Further, the Examiner cites Habener for providing the motivation to produce GLP-1. Applicants do not dispute that Habener teaches the potential therapeutic activity of GLP-1 in treating diabetes. However, the Examiner has not pointed to any specific motivation in any of the cited references, to combine the teachings of Habener with those of the other references, in such a manner as to arrive at the specific constructs for production of GLP-1 as recited in the rejected claims. The fact that producing GLP-1 (or any other specific small peptide) might be generally desirable does not provide a motivation to make any one specific method or construct for producing it. The Examiner has provided no evidence of a specific motivation to produce the claimed constructs. A showing of a suggestion, teaching, or motivation to combine "must be clear and particular...Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" In re Dembiczack, 175 F.3d 994 (Fed. Cir. 1999). Thus, the Examiner's broad, generic basis for finding the required motivation is insufficient.

Therefore, the Examiners' basis for finding both a motivation and reasonable expectation of success to arrive at the claimed constructs is traversed. In addition, the claimed constructs have the surprising property that they allow expression in a non-endocrine cell.

II. Cell claims

Claims 14, 17, 19, 21-35, 37-46 and 83-89 are rejected as unpatentable over Sevarino in view of Stoller, Habener, Susuki and Patel, and further in view of newly cited Warren et al. and Selden et al. (US 6,531,124). This rejection is respectfully traversed. None of the cited

references, alone or in combination, suggest making a non-endocrine cell that expresses a fusion of the pro-region of somatostatin with any heterologous small peptide, much less GLP-1 or any other peptide specifically recited in the claims.

Sevarino, Stoller, Habener, Susuki and Patel were previously discussed in the first Reply. Sevarino discloses a construct encoding a chimera of the pre-pro region of a rat somatostatin and the C-terminus of anglerfish somatostatin, expressed in AtT20 and RIN 5F cells (both endocrine secretory cell lines). Stoller describes a construct encoding a chimera of the pre-pro region of somatostatin and α-globin expressed in rat pituitary tumor (endocrine) GH3 cells. Habener teaches that GLP-1 is a potential therapeutic agent for treatment of diabetes and teaches production of GLP-1 by "conventional means such as by the well-known solid-phase peptide synthesis...by fragmenting the naturally occurring amino acid sequence, using for example, a proteolytic enzyme...or through recombinant DNA technology" (column 4, line 68-column 5, line 12 of Habener et al.). Susuki describes a method for producing a chimeric protein that can be cleaved and efficiently produced as an inclusion body in *E. coli* under large scale culture (Susuki 2:6-11). Patel teaches that mammalian pro-protein convertases such as furin, PACE4, and PC1-6, mediate endoproteolysis of prosomatostatin and Patel also teaches that "PC-12 cells were similar to COS-7 cells in that they exhibited inefficient constitutive processing of prosomatostatin". The Examiner acknowledges that "none of them teach recombinant expression of a small peptide such as GLP-1 in a non-endocrine cell." (Office Action, page 12.)

The Examiner has now combined the above references with Warren and Selden to provide the element of "non-endocrine cell". Warren teaches expression of preprosomatostatin in COS cells, which are non-endocrine cells. Selden discloses primary and secondary cells transfected with a GLP-1 encoding DNA sequence. The Examiner argues that a motivation to combine Warren and Selden with the other references exists because "Warren has demonstrated successful expression of somatostatin by transfecting preprosomatostatin gene into a non-endocrine cell; Selden has demonstrated successful expression of GLP-1 in a non-endocrine cell."

This rejection is traversed. None of the references, alone or in any combination, provide a motivation or suggestion to link the pro-region of somatostatin to a non-somatostatin small peptide in a non-endocrine cell, as claimed. The fact that Selden discloses expressing GLP-1

using a primary (presumably non-endocrine) cell transfected with a DNA encoding GLP-1 does not provide a suggestion or motivation to produce the claimed cell having the specific recited construct. One method of producing a particular peptide does not make obvious a completely unrelated method of producing the same peptide. Nothing in Selden suggests that GLP-1 can be produced in a non-endocrine cell by linking GLP-1 to the somatostatin pro-region. Moreover, Warren does not add anything to the references already cited in the first Office Action since Patel (cited in the first Office Action and discussed in the first Reply) also discloses expression of prosomatostatin in COS cells. If anything, both Patel and Warren in fact teach away from the claimed cells, as discussed below.

Warren discloses expression of prosomatostatin in COS cells but notes: "Our data show a relatively low level of [somatostatin] secreted compared to insulin secretion from AtT-20 cells." (Warren at page 553, 2d column, emphasis added.) As noted in the first Reply, Patel (which has a publication date about 9 years after Warren and is therefore more representative of the state of the art) notes the highly inefficient cleavage of prosomatostatin to somatostatin in non-endocrine cell types, including COS cells. In particular, Patel discloses that about 60% of total prosomatostatin remained unprocessed in the non-endocrine cells COS-7 and PC-12 (compared to almost no unprocessed somatostatin in endocrine cells AtT-20 and GH3, see Figure 2), suggesting that non-endocrine cells lack the proper machinery to efficiently process prosomatostatin into the mature form. Thus, in view of Patel, and further in view of Warren's earlier observation that somatostatin produced in a non-endocrine cell (a COS cell) was secreted at a low level, the skilled artisan would have no motivation or reasonable expectation of success to produce a non-somatostatin small peptide by expressing the small peptide linked to the proregion of somatostatin in a non-endocrine cell. The combination of cited references simply provides no expectation that such a heterologous small peptide would be efficiently processed and secreted given that even somatostatin is not efficiently processed and/or secreted in non-endocrine cells when linked to its own pro-region. Accordingly, claims 14, 17, 19, 21-35, 37-46 and 83-89 are patentable over the cited references.

Enclosed is a Petition for Extension of Time along with the required fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: March 3, 2004

Leda Trivinos
Reg. No. 50,635

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906